

REMARKS

Reexamination and reconsideration of the above-referenced patent application in light of the foregoing proposed amendments to the claims and the following remarks is respectfully requested.

Claims 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 are pending in this application. Claims 2-20, 22, 25, 27-30, 32, 33, 36, 38 and 42 have been canceled without prejudice or disclaimer. Claims 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 have been amended. No new claims have been added. The amendments do not introduce new matter. The amended claims have been limited to a method of screening using the co-ordinates of IGF-1R provided in Fig. 1. Clear support for the amendments and the concept of screening for agonists of IGF-1R can be found in the following passages from the specification:

Accordingly, in a first aspect the present invention provides a method of designing a compound able to bind to a molecule of the insulin receptor family and to modulate an activity mediated by the molecule, including the step of assessing the stereochemical complementarity between the compound and the receptor site of the molecule, wherein the receptor site includes:

- (a) amino acids 1 to 462 of the receptor for IGF-1, having the atomic coordinates substantially as shown in Figure 1;
- (b) a subset of said amino acids, or;
- (c) amino acids present in the amino acid sequence of a member of the insulin receptor family, which form an equivalent three-dimensional structure to that of the receptor molecule as depicted in Figure 1. [Page 6, lines 3-13.]

* * *

In a further preferred embodiment of the first aspect of the present invention, the compound has the ability to increase an activity mediated by the receptor molecule. [Page 7, lines 16-18.]

* * *

In a further preferred embodiment, the computer-assisted method is used to identify potential compounds which have the ability to increase an activity mediated by the receptor molecule. [Page 8, lines 23-25.]

* * *

In another preferred embodiment, the computer-assisted method further includes the step of obtaining a molecule with a chemical structure selected in steps (d) and (e), and testing the compound for the ability to increase an activity mediated by the receptor. [Page 8, lines 26-29.]

* * *

In a third aspect, the present invention provides a method of screening of a putative compound having the ability to modulate the activity of a receptor of the insulin receptor family, including the steps of identifying a putative compound by a method according to the first or second aspects, and testing the compound for the ability to increase or decrease an activity mediated by the receptor. [Page 8, line 32 to page 9, line 2.]

* * *

Accordingly, agonists or antagonists which bind to a portion of the residues lining the groove are encompassed by the present invention. [Page 14, lines 7 - 8.]

* * *

The structure of IGF receptor can be considered as a filter or screen to design, or evaluate, potential ligands for the receptor. Those skilled in the art can use a number of well known methods for *de novo* ligand design, such as GRID, GREEN, HSITE, MCSS, HINT, BUCKETS, CLIX, LUDI, CAVEAT, SPLICE, HOOK, NEWLEAD, PRO_LIGAND, ELANA, LEGEND, GenStar, GrowMol, GROW, GEMINI, GroupBuild, SPROUT, and LEAPFROG, to generate potential agonists or antagonists for IGF-1R. In addition, the IGF-1R structure may be used as a query for database searches for potential ligands. [Page 45, lines 14 - 20.]

The specification also provides adequate methods by which compounds identified by the screening method of the invention can be assessed for agonist and antagonist activity using *in vitro* or *in vivo* assays of hormone function (see, for example, page 17, line 3 to page 18, line 7 and page 28, line 11 to page 31, line 16). A person of skill in the art would immediately understand that the binding affinity assays or cell-based assays described in these sections of the specification could be readily used to identify agonists and antagonists of IGF-1R.

Applicants note the Examiner's acceptance of the drawing corrections to Figs. 1, 2 and 9. The Examiner noted that Applicants' response submitted August 6, 2003 did not address the objections to the drawings with respect to Figs. 3-8, 10 and 11. A copy of the Notice of Draftperson's Patent Drawing Review, as received by the undersigned, is attached to this response as Exhibit A. The top section pertaining to the aforementioned drawing figures was crossed out by

someone in the USPTO and specific comments were entered in the comments section with respect to Figs. 1 and 9. Since the top section was crossed out, it was believed that the objections raised in the top section of the Notice were entered in error and that Applicants only needed to comply with the objections set forth in the comments section of the form. Clarification is requested.

Rejection Under 35 U.S.C. § 101

Claims 1 and 34-43 were rejected under 35 U.S.C. § 101. Claims 36, 38 and 42 have been canceled, thereby rendering the rejection as to these claims moot. According to the Examiner, the claimed invention with respect to claims 1, 34, 35, 37, 39-41 and 43 is "directed to non-statutory subject matter." The Examiner states that "[t]o the degree that the method of claims 1 and 47 are directed to a completely *in silico* method where the obtaining and testing steps are computational in nature rather than laboratory chemistry ..., the claims are considered to be non-statutory as they merely manipulate data." Applicant respectfully disagree.

Claim 1 is not a "completely *in silico* method." The claimed method as set forth in amended claim 1 recites step C which requires testing the compound *in vivo* or *in vitro* for its ability to either modulate binding of a ligand to the IGF-1R insulin receptor or to modulate signal transduction by binding to the IGF-1R receptor. Support for the amendments can be found at page 8, lines 3-8, 19-22 and page 9, lines 3-8 of the specification. In order to emphasize step C, claim 1 has been further amended to add step D to select a compound tested in step C that has the abilities required by step C. These are not computational steps or manipulating data. They are physical and chemical steps.

It is not clear from the Examiner's remarks whether claim 47 was intended to be included in this rejection. Assuming, arguendo, that claim 47 is also rejected under 35 U.S.C. § 101, the arguments above for the patentability of claim 1 are equally applicable to claim 47; e.g., compounds that meet the criteria of steps A and B are selected in step C upon experimental determination of the desired K_d or K_I .

For the foregoing reasons it is respectfully requested that the rejection of claims 1 and 34-43 under 35 U.S.C. § 101 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 21, 23, 24, 26, 30-32 and 34-49 were rejected under 35 U.S.C. § 112, first paragraph. Claims 30, 32, 36, 38 and 42 have been canceled, thereby rendering the rejection as to these claims moot. According to the Examiner, claims 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 fail "to comply with the written description" requirement on the following grounds.

The Examiner finds that there is no basis in the specification for the phrase "modulates binding of a natural ligand" in claim 1 and to require testing the compound for its ability to modulate the binding. Applicants respectfully traverse this rejection. With regard to the phrase "modulates binding of a natural ligand," the term 'natural ligand' has been replaced with a list of natural IGF-1R ligands. The listed ligands are recited in the specification on page 4, lines 21-22 and are well known as of the priority date of this application. They are also recited in the references cited throughout the specification.

The Examiner also finds no written descriptive support in claim 1 for the phrase "modulates signal transduction via IR, IGF-1R or IRR" and for testing the compound for its

ability to modulate the binding. Claim 1 has been amended and is now limited to a method of screening using the co-ordinates of IGF-1R only as provided in Fig. 1. As for the written description for "testing the compound for its ability to modulate binding," the specification in the paragraph bridging pages 17 and 18 of the specification describes selecting the compound and testing the ability of the compound to antagonize signal transduction using routine cellular assays. Accordingly, the specification provides sufficient written descriptive support for the testing of the compound's ability to modulate binding.

With regard to support for claim 34, support for this claim is provided at page 17, lines 28-31 of the specification. The claim is dependent on claim 1 and requires in step (C)(ii) the testing of the compound for its ability to modulate IGF-1R mediated cell proliferation. The specification discloses at page 17, lines 28-31 that "[o]nce [the] candidate compounds have been identified, their ability to antagonize signal transduction via the IGF-1R can be assessed using a number of routine *in vitro* cellular assays such as inhibition of IGF-1 mediated cell proliferation." Accordingly, claim 34 is supported by the specification of the present application.

The Examiner has further rejected claims 1, 21, 23, 24, 26, 31 and 34-49 under 35 U.S.C. § 112, first paragraph, as not satisfying the enablement requirement of the statute. Claims 36, 38 and 42 have been canceled, thereby rendering the rejection as to these claims moot. With regard to claims 1, 21, 23, 24, 31, 34, 35, 37, 39-41 and 43-49, the Examiner finds that the "specification does not exemplify modeling of any compound and a molecule as defined by [claim 1, step (A)(i)-(iii)]" and that the "specification does not disclose any compounds meeting

the structural and functional limitations required by the claims." Applicants respectfully traverse this rejection.

The test for enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation. *United States V. Telecommunications, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529 F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). It is the function of the specification, not the claims, to set forth the practical limits of operation of an invention. *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). The Examiner has not established that undue experimentation would be required for a person having ordinary skill in the art to practice the claimed invention.

Independent claims 1 and 47 have been amended to delete step (A)(iii). Examples exemplifying specific compounds or molecules for step (A)(i)-(ii) of claims 1 and 47 are not required to support enablement. The specification, as a whole, must be considered to determine if the invention as disclosed is enabled. The invention is directed to a method of identifying a compound that possesses stereochemical complementarity with the molecule as well as possessing the ability to modulate IGF-1R. The Examiner has not presented any evidence to

show that this concept would require undue experimentation by a person skilled in the art to practice the claimed invention in the absence of a recitation of specific compounds.

The Examiner made a finding that "the claims can be considered to be effectively no different from obtaining and testing all potential compounds as all assessed compounds will be obtained and tested." Claim 1 has been amended so that step (B) recites: "selecting and obtaining a compound assessed in step (A) which possesses stereochemical complementarity to the molecule." Not all molecules assessed in step (A) will exhibit stereochemical complementarity to the receptor molecule. Step (B), as amended, would require a selection from all of the compounds tested, a compound or compounds exhibiting stereochemical complementarity to the receptor. Those compounds selected in step (B) are then subjected to further *in vitro* or *in vivo* testing. Therefore, contrary to the Examiner's position, not all compounds obtained in step (B) will be subject to further testing in step (C).

The Examiner also made a finding that the claims do not recite any scoring function or cut-off value to discriminate high ranking compounds from low ranking compounds. It is not necessary to provide these cut-off values, particularly in view of the requirement of a selection being made. The concept of "selecting" relates to a choice being made with respect to the best or most suitable compounds in terms of stereochemical complementarity to the molecule of present interest.

The Examiner made a finding that "the specification does not clearly specify what is required to be performed in assessing 'stereochemical complementarity'". In particular, the Examiner asserts that the specification does not provide a specific definition of "stereochemical

complementarity". The Examiner acknowledges that page 6 of the specification discusses "stereochemical complementarity" in the context of "lock-and-key" visualization, but finds the additional references to "matching intra-site coordinates lining the groove of the particular receptor site" (page 13) and the optimal "fit" (page 14) do not make it clear that the discussions on pages 6, 13 and 14 of these terms are "intended to be embraced by the claims."

The terms "stereochemical complementarity", "matching intra-site surface coordinates" and "optimizing, geometrically or chemically, the fit" are all synonymous terms and are commonly used in the art. The phrase 'stereochemical complementarity' was already well known in the art before the priority date of the present application. For example, a search of the PubMed database using the term "stereochemical complementarity" yielded 31 references. See the list of references attached to this response as Exhibit B. Some examples of these references are set out below:

1. Bransome, E.D. et al.; "Apparent stereochemical complementarity of estrogens and helical cavities between DNA base pairs: implications for the mechanism of action of steroids," *J. Theor. Biol.* 1985 Jan 7; **112**(1):97-108.
2. Hendry, L.B.; "Drug design with a new type of molecular modeling based on stereochemical complementarity to gene structure," *J. Clin. Pharmacol.* 1993 Dec; **33**(12):1173-87.
3. Hendry, L.B. and Mahesh V.B.; "Stereochemical complementarity of progesterone, RU486 and cavities between base pairs in partially unwound double stranded DNA

assessed by computer modelling and energy calculations, " *J. Steroid Biochem. Mol. Biol.* 1992; 41:647-651.

Applicants also note that the terms "stereochemical fit" and "shape complementarity" are recited in the claims in U.S. Patent Nos. 4,461,619 and 6,184,241. Copies of the patents are attached as Exhibits C and D, respectively. For example, claim 1 of U.S. Patent No. 4,461,619 defines a method for determining the biological activity of a molecule which includes comparing the stereochemical properties of the molecule with respect to cavities in a nucleic acid complex to determine a "complementary fit", with a fit indicating the biological activity. Further, claim 1 of U.S. Patent No. 6,184,241 defines an aspartic protease/inhibitor complex wherein a portion of the complex has a "shape complementarity" with at least a portion of the substrate binding site of the aspartic protease. A person skilled in the art would have understood that the concepts of "stereochemical fit" and "shape complementarity" are synonymous with "stereochemical complementarity."

The Examiner asserts that the specification does not clearly imply what is required to be performed in assessing stereochemical complementarity. The Applicants submit that this is covered by reference to the docking programs as set forth on pages 14-16 of the specification. These programs take each chemical compound and calculate the strength of its interaction with the selected binding site on the IGF-1R by calculating the H-bonds, the geometric shape complementarity, the hydrophobic interactions, the Van der Waals forces and the salt bridges. All of these parameters contribute to the strength of the interaction. Each compound is placed in a large number of orientations and the calculated strengths of these parameters are recorded for

each orientation. A person of ordinary skill in the art would clearly understand what is required to be performed in assessing stereochemical complementarity in light of the references provided in the specification.

The Examiner contends that the claims "do not contain limitations to cavities, binding sites, or energy optimization." The Examiner concludes that, in the absence of such limitations, a person having ordinary skill in the art would not have known "what positive, active steps must be performed to meet these limitations." Applicants respectfully traverse. The Examiner has not explained her basis as to why these alleged limitations must be present in the claims. Further, the Examiner has not presented any evidence or cogent scientific reasoning to support her conclusion.

The Examiner also contends that the claims do not "require finding a binding pocket, using a known binding pocket or using a docking program" and that the claims are not limited accordingly. The Examiner has neither explained why nor presented any cogent scientific reasoning as to why any of these are necessary limitations that must be included in the claims. The finding of a suitable binding site is inherent in the claim language. For example, a person skilled in the art would understand that the phrase "assessing the stereochemical complementarity between the compound and a molecule" requires a comparison between the size and shape of a binding pocket within the molecule and a putative ligand. The Examiner's attention is directed to the Ring et al. (1993) paper which was submitted as Exhibit C with Applicants' response dated August 6, 2003. The paper describes using the Dock program to

select ligands "with the best shape-complementarity scores" when compared to a three-dimensional models of proteases.

The claims require assessing the complementarity between the compound and the receptor molecule. The original claim language referred to assessing the stereochemical complementarity between the compound and a "topographic region" of the molecule. It is Applicants' position that the "topographic region" referred to a potential binding site on the receptor molecule. At the interview with the Examiner last year on June 24, 2003, the Examiner suggested simply removing the term "topographic region" on the ground that the phrase "assessing the stereochemical complementarity between the compound and molecule" was clearer. We adopted the Examiner's suggestion and amended the claim accordingly.

The Examiner also rejected claims 21, 23-24 and 26 which are directed to computer-assisted methods for identifying potential compounds. The Examiner states that the specification provides no guidance on what a criteria data set must include or how it is generated. The Examiner also contends that the specification does not identify any database that could be used in the method as claimed. The way in which the criteria data set is generated is clear from the claim language. In particular, it would be clear to a person having ordinary skill in the art that the criteria data set generated represents a three-dimensional structure that has stereochemical complementarity with the IGF-1R molecule. This criteria data set is then compared with chemical structures stored in a database. As explained in the specification at page 15, lines 3-9, databases such as the Cambridge Structural Database System or the Protein Data Bank can be searched for molecules which approximate the shape defined by the "criteria data set".

For all of the foregoing reasons, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claim 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 21, 23, 24, 26, 30-32 and 34-49 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 30, 32, 36, 38 and 42 have been canceled, thereby rendering the rejection as to these claims moot. The Examiner made a finding that claim 1 is unclear with respect to the phrases "natural ligand" and "signal transduction via IR, IGF-1R or IRR." The objected to term "natural" has been deleted from the phrase "natural ligand." As for the other phrase, the receptor has been limited to IGF-1R and the phrase has been amended to recite that the signal transduction is modulated by binding to IGF-1R. It is believed that by these amendments, the rejection of claim 1 is overcome.

The Examiner found that the phrases "substantially as shown" and "form an equivalent three-dimensional structure" to be indefinite and unclear. The Examiner's Advisory Action states that the Section 112 rejections are maintained because the specification does not provide definitions for the phrases "natural ligand" and "equivalent three-dimensional structure". These phrases have been deleted from the claims and, accordingly, these rejections are overcome.

The Examiner found that the phrase "which are structurally similar to a portion of said criteria data set" in claim 21 is unclear because "[i]t is unknown how much of the criteria data set constitutes 'a portion'." The phrase in claim 21 has been amended to delete the objected to term

"a portion of" so that the phrase as amended reads: "which are structurally similar to said criteria data set." It is believed that by this proposed amendment, the rejection is overcome.

The Examiner rejected claims 23 and 24 on the basis that the phrase "selected in steps (d) and (e)" is unclear. In order to obviate this rejection, the phrase has been amended to read: "selected in step (d) or outputted in step (e)." It is believed that by this amendment that the rejection to the phrase is overcome.

Claims 35, 37 and 38 have been rejected on the basis that there is no antecedent basis for "or more subsets". Claim 38 has been canceled, thereby rendering the rejection as to this claim moot. Claims 35 and 37 have been amended to change the phrase "one or more subsets" to -- subset--. It is believed that by this amendment, the rejection is overcome.

The Examiner found that claims 39 and 40 are "confusing in adding the step of modifying the compound" because the claims do "not make clear if this is performed before or after obtaining in step (B) or before or after testing in step (C)." It is proposed to add the phrase "selected in step (B) or step (D)" to obviate the rejection by the Examiner.

Finally, the Examiner has objected to claim 47 as being unclear because it is not clear whether the K_d or K_I is "a predicted, calculated or experimentally determined value." It is proposed to amend claim 47 to specify that the K_d and K_I are "experimentally determined." Also, it is proposed to amend claims 47 and 48 to correct an obvious error to change K_b to K_d .

For all of the foregoing reasons, it is respectfully requested that the rejection of claims 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

CONCLUSION

It is submitted that the claims 1, 21, 23, 24, 26, 31, 34, 35, 37, 39-41 and 43-49 are in compliance with the provisions of 35 U.S.C. § 101, and the first and second paragraphs of 35 U.S.C. § 112. Accordingly, favorable reconsideration of the claims is requested in light of the amendments to the claims and the foregoing remarks. It is requested that the proposed amendments be entered. Allowance of the claims is courteously solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due under 37 C.F.R. § 1.17 and in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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NOTICE OF DRAFTSPERSON'S
PATENT DRAWING REVIEWThe drawing(s) filed (insert date) 8-50-01 are:

approved by the Draftsperson under 37 CFR 1.84 or 1.152.
 objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be submitted according to the instructions on the back of this notice.

<p>1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: <input type="checkbox"/> Black ink. Color. <input type="checkbox"/> Color drawings are not acceptable until petition is granted. <input type="checkbox"/> Fig(s) _____</p> <p><input type="checkbox"/> Pencil and non black ink not permitted. Fig(s) _____</p> <p>2. PHOTOGRAPHS. 37 CFR 1.84(b): <input type="checkbox"/> full-tone set is required. Fig(s) _____ <input type="checkbox"/> Photographs may not be mounted. 37 CFR 1.84(e) <input type="checkbox"/> Poor quality (half-tone). Fig(s) _____</p> <p>3. TYPE OF PAPER. 37 CFR 1.84(e): <input type="checkbox"/> Paper not flexible, strong, white, and durable. <input type="checkbox"/> Fig(s) _____ <input type="checkbox"/> Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) _____ <input type="checkbox"/> Mylar, velum paper is not acceptable (too thin). <input type="checkbox"/> Fig(s) _____</p> <p>4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes: <input type="checkbox"/> 21.0 cm by 29.7 cm (DIN size A4) <input type="checkbox"/> 21.6 cm by 27.9 cm (8 1/2 x 11 inches) <input type="checkbox"/> All drawing sheets not the same size. <input type="checkbox"/> Sheet(s) _____ <input type="checkbox"/> Drawings sheets not an acceptable size. Fig(s) _____</p> <p>5. MARGINS. 37 CFR 1.84(g): Acceptable margins: Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: A4 Size Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: 8 1/2 x 11 Margins not acceptable. Fig(s) _____ <input type="checkbox"/> Top (T) <input type="checkbox"/> Left (L) <input type="checkbox"/> Right (R) <input type="checkbox"/> Bottom (B)</p> <p>6. VIEWS. 37 CFR 1.84(h): REMINDER: Specification may require revision to correspond to drawing changes. Partial views. 37 CFR 1.84(h)(2) <input type="checkbox"/> Brackets needed to show figure as one entity. <input type="checkbox"/> Fig(s) _____ <input type="checkbox"/> Views not labeled separately or properly. <input type="checkbox"/> Fig(s) <u>1-9</u> <input type="checkbox"/> Enlarged view not labeled separately or properly. <input type="checkbox"/> Fig(s) _____</p> <p>7. SECTIONAL VIEWS. 37 CFR 1.84(h)(3): <input type="checkbox"/> Hatching not indicated for sectional portions of an object. <input type="checkbox"/> Fig(s) _____ <input type="checkbox"/> Sectional designation should be noted with Arabic or Roman numbers. Fig(s) _____</p>	<p>8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i): <input type="checkbox"/> Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____</p> <p>9. SCALE. 37 CFR 1.84(k): <input type="checkbox"/> Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. <input type="checkbox"/> Fig(s) _____</p> <p>10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l): <input type="checkbox"/> Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). <input type="checkbox"/> Fig(s) <u>3-8, 10</u></p> <p>11. SHADING. 37 CFR 1.84(m): <input type="checkbox"/> Solid black areas/pale. Fig(s) _____ <input type="checkbox"/> Solid black shading not permitted. Fig(s) _____ <input type="checkbox"/> Shade lines pale, rough and blurred. Fig(s) _____</p> <p>12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p): <input type="checkbox"/> Numbers and reference characters not plain and legible. <input type="checkbox"/> Fig(s) <u>1-11</u> <input type="checkbox"/> Figure legends are poor. Fig(s) <u>1-11</u> <input type="checkbox"/> Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) <input type="checkbox"/> Fig(s) _____ <input type="checkbox"/> English alphabet not used. 37 CFR 1.84(p)(2) <input type="checkbox"/> Figs _____ <input type="checkbox"/> Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) <input type="checkbox"/> Fig(s) _____</p> <p>13. LEAD LINES. 37 CFR 1.84(q): <input type="checkbox"/> Lead lines cross each other. Fig(s) _____ <input type="checkbox"/> Lead lines missing. Fig(s) _____</p> <p>14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t): <input type="checkbox"/> Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) _____</p> <p>15. NUMBER OF VIEWS. 37 CFR 1.84(u): <input type="checkbox"/> Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____</p> <p>16. CORRECTIONS. 37 CFR 1.84(w): <input type="checkbox"/> Corrections not made from prior PTO-948 dated _____</p> <p>17. DESIGN DRAWINGS. 37 CFR 1.152: <input type="checkbox"/> Surface shading shown not appropriate. Fig(s) _____ <input type="checkbox"/> Solid black shading not used for color contrast. Fig(s) _____</p>
<p>COMMENTS FIG. 1 SHOULD BE LABELED AS FIG. 1, FIG. 1A-1, FIG. 1A-3 AND SO-ON UNTIL ALL OF FIGURE 1 HAS BEEN LABELED.</p> <p>FIG. 9 SHOULD BE LABELED AS FIG. 9A, 9B</p>	

REVIEWER J. Christ DATE 11-5-02 TELEPHONE NO. 703 305-2436ATTACHMENT TO PAPER NO. 20

Reference List

1. Behe, M. J.; Lattman, E. E., and Rose, G. D. The protein-folding problem: the native fold determines packing, but does packing determine the native fold? *Proc Natl Acad Sci U S A.* 1991 May 15; 88(10):4195-9.
2. Boucherle, A.; Fillion, H., and Cousse, H. [Contribution of stereochemistry to the study of the spatial organization of pharmacological receptors]. *J Pharmacol.* 1986; 17 Suppl 2:44-58.
3. Bransome, E. D. Jr; Hendry, L. B.; Muldoon, T. G.; Mahesh, V. B.; Hutson, M. S., and Campbell, L. K. Apparent stereochemical complementarity of estrogens and helical cavities between DNA base pairs: implications for the mechanism of action of steroids. *J Theor Biol.* 1985 Jan 7; 112(1):97-108.
4. Celikel, R.; Madhusudan; Varughese, K. I.; Shima, M.; Yoshioka, A.; Ware, J., and Ruggeri, Z. M. Crystal structure of NMC-4 fab anti-von Willebrand factor A1 domain. *Blood Cells Mol Dis.* 1997; 23(1):123-34.
5. Edmundson, A. B. and Ely, K. R. Binding of N-formylated chemotactic peptides in crystals of the Mcg light chain dimer: similarities with neutrophil receptors. *Mol Immunol.* 1985 Apr; 22(4):463-75.
6. Harris, L. F.; Sullivan, M. R., and Hatfield, D. L. Directed molecular evolution. *Orig Life Evol Biosph.* 1999 Aug; 29(4):425-35.
7. Hendry, L. B. Drug design with a new type of molecular modeling based on stereochemical complementarity to gene structure. *J Clin Pharmacol.* 1993 Dec; 33(12):1173-87.
8. ---. Stereochemical complementarity of DNA and steroid agonists and antagonists. *J Steroid Biochem.* 1988 Oct; 31(4B):493-523.
9. Hendry, L. B.; Bransome, E. D. Jr; Lehner, A. F.; Muldoon, T. G.; Hutson, M. S., and Mahesh, V. B. The stereochemical complementarity of DNA and reproductive steroid hormones correlates with biological activity. *J Steroid Biochem.* 1986 Apr; 24(4):843-52.
10. Hendry, L. B. and Mahesh, V. B. Stereochemical complementarity of progesterone and cavities between base pairs in partially unwound double stranded DNA using computer modeling and energy calculations to determine degree of fit. *J Steroid Biochem Mol Biol.* 1991 Aug; 39(2):133-46.
11. ---. Stereochemical complementarity of progesterone, RU486 and cavities between base pairs in partially unwound double stranded DNA assessed by computer modelling and energy calculations. *J Steroid Biochem Mol Biol.* 1992 Mar; 41(3-8):647-51.
12. Hendry, L. B.; Muldoon, T. G., and Mahesh, V. B. The metabolic pathways for hormonal steroids appear to be reflected in the stereochemistry of DNA. *J Steroid Biochem Mol Biol.* 1992 Aug; 42(7):659-70.

13. ---. Stereochemical complementarity between antiestrogens and DNA. *Adv Exp Med Biol.* 1987; 219:743-7.
14. Heywood, B. R. Biominerization: new directions in crystal science. *Microsc Res Tech.* 1994 Apr 1; 27(5):376-88.
15. Kajava, A. V.; Bogdanov, M. V., and Nesmeyanova, M. A. Stereochemical analysis of interaction of signal peptide with phospholipids at the initiation of protein translocation across the membrane. *J Biomol Struct Dyn.* 1991 Aug; 9(1):143-57.
16. Korolkovas, A. [Action of hormones at the molecular level]. *Rev Paul Med.* 1973 Mar; 81(3):169-78.
17. Lee, A. Y.; Smitka, T. A.; Bonjouklian, R., and Clardy, J. Atomic structure of the trypsin-A90720A complex: a unified approach to structure and function. *Chem Biol.* 1994 Oct; 1(2):113-7.
18. Lee, M.; Chang, D. K.; Pon, R. T., and Lown, J. W. Sequence dependent conformation and local geometry of the conserved branch site sequence element d(TpApCpTpApApC), essential for yeast mRNA splicing, deduced from high resolution ¹H-NMR. *J Biomol Struct Dyn.* 1987 Aug; 5(1):35-46.
19. Matta, C. F. and Bader, R. F. Atoms-in-molecules study of the genetically encoded amino acids. III. Bond and atomic properties and their correlations with experiment including mutation-induced changes in protein stability and genetic coding. *Proteins.* 2003 Aug 15; 52(3):360-99.
20. Muller, G.; Gurrath, M., and Kessler, H. Pharmacophore refinement of gpIIb/IIIa antagonists based on comparative studies of antiadhesive cyclic and acyclic RGD peptides. *J Comput Aided Mol Des.* 1994 Dec; 8(6):709-30.
21. Mylvaganam, S. E.; Paterson, Y., and Getzoff, E. D. Structural basis for the binding of an anti-cytochrome c antibody to its antigen: crystal structures of FabE8-cytochrome c complex to 1.8 Å resolution and FabE8 to 2.26 Å resolution. *J Mol Biol.* 1998 Aug 14; 281(2):301-22.
22. Parhami-Seren, B.; Kussie, P. H.; Strong, R. K., and Margolies, M. N. Conservation of binding site geometry among p-azophenylarsonate-specific antibodies. *J Immunol.* 1993 Mar 1; 150(5):1829-37.
23. Pastor, N.; Pardo, L., and Weinstein, H. Does TATA matter? A structural exploration of the selectivity determinants in its complexes with TATA box-binding protein. *Biophys J.* 1997 Aug; 73(2):640-52.
24. Prieur, B. A stereochemical relationship could explain the origin of the genetic code. *C R Acad Sci III.* 1992; 314(6):245-52.
25. Rowland, M. J.; Bransome, E. D. Jr, and Hendry, L. B. Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J Clin Pharmacol.* 1994 Jan; 34(1):80-5.

26. Überoi, N. K.; Hendry, L. B.; Muldoon, T. G.; Myers, R. B.; Segaloff, A.; Bransome, E. D., and Mahesh, V. B. Structure-activity relationships of some unique estrogens related to estradiol are predicted by fit into DNA. *Steroids*. 1985 Mar-1985 Apr 30; 45(3-4):325-40.
27. Warwicker, J. Investigating protein-protein interaction surfaces using a reduced stereochemical and electrostatic model. *J Mol Biol*. 1989 Mar 20; 206(2):381-95.
28. Westall, F. C. and Root-Bernstein, R. S. An explanation of prevention and suppression of experimental allergic encephalomyelitis. *Mol Immunol*. 1983 Feb; 20(2):169-77.
29. Williams, R. M. and Jones, R. Specificity of binding of zona pellucida glycoproteins to sperm proacrosin and related proteins. *J Exp Zool*. 1993 May 15; 266(1):65-73.
30. Wust, M. and Croteau, R. B. Hydroxylation of specifically deuterated limonene enantiomers by cytochrome p450 limonene-6-hydroxylase reveals the mechanism of multiple product formation. *Biochemistry*. 2002 Feb 12; 41(6):1820-7.
31. Yamashita, A.; Kato, H.; Wakatsuki, S.; Tomizaki, T.; Nakatsu, T.; Nakajima, K.; Hashimoto, T.; Yamada, Y., and Oda, J. Structure of tropinone reductase-II complexed with NADP⁺ and pseudotropine at 1.9 Å resolution: implication for stereospecific substrate binding and catalysis. *Biochemistry*. 1999 Jun 15; 38(24):7630-7.